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RELATIVE BIOLOGICAL EFFECTIVENESS OF VARIOUS TYPES OF RADIATIONS

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on such effects as chromosome aberrations, somatic effects, and survival of animal cells, the authors arrived at the conclusion that the RBE increases as the absorbed dose decreases.

Results of a study of the dose-effect curves for radiations with low and high LEL are of great interest. A comparison of the data obtained with α radiation and neutrons of the fission spectrum, with the data on X-ray and γ irradiation for the survival of mammal cells [19, 20] is illustrated by the dose-effect curves in Fig. 2. It is usually believed that the curve for radiation with high LEL (50 keV/μ and more) is more linear in a semilogarithmic scale. Berry [21] obtained a dose-effect curve for 14 MeV monoenergetic neutrons (LEL = 20 keV/μ), intermediate between the curve for fission neutrons (LEL = 50 keV/μ) and 200 kV X-rays (0.5-2.5 keV/μ). According to these results, just as in a study of chromosome aberrations, there is a linear component in the dose-effect curve for radiation with high LEL, whereas the curve of radiations with low LEL possesses a linear member and nonlinear members of higher order.

In experiments in which enzymes, viruses, and certain bacterial species were investigated, the dose-effect curves become linear in a semilogarithmic scale for all LEL. In most of the studies it has been found that the RBE decreases with increasing LEL [22], but according to other data, the RBE increases with increasing LEL, reaching very high values [23].

Influence of the Time Factor on the RBE

A substantial influence upon the biological effect may be exerted by the distribution of the dose with time (time factors). In radiobiology, the time factor is considered to be the change in the biological effect of radiation with changing dose rate or when a summary dose is broken down into individual fractions, differing in magnitude and administered at various intervals.

The influence of the dose rate of X-ray and γ-radiations on the biological effect is established experimentally.

The work of Bateman [24] cites data on the influence of the dose rate of X-ray and γ radiations (low LEL) on the value of $LD_{50/30}$ for rats and mice. When the dose rate is increased from 0.2 to 1000 rad/min, the value of $LD_{50/30}$ decreases by 2.4-fold; consequently, the effectiveness of radiation with high dose rate increases.

Rather exhaustive information on the influence of dose rate upon genetic factors is cited by Fritz-Niggli [25]. A change in the dose rate is capable of changing the frequency of mutations in mice. Under the influence of X-rays (250 kV) on male mice at a dose rate of 80 R/min, the number of mutations per locus per 100,000 gametes was 13.29, while at a dose rate of 100 R/week it was 1.37. Thus, a protracted influence is less effective, evidently because at these intensities a larger number of fragments are recombined into the former chromosome.

An analogous tendency for an increase in the effect with increasing dose rate is also observed for processes of cell division [25, 26].

A different effect occurs under the action of neutrons [27]. The

biological effect of neutrons does not depend upon the dose rate within a broad range of dose rates ($15 \cdot 10^{-2}$ -- $2 \cdot 10^{8}$ rad/min) [28].

The effect of a change in the duration of exposure may also be explained by primary processes in the irradiated water [25]. At a high dose rate, more uniformly distributed radicals arise, which partly form active peroxides, whereas the ability of the active radicals that arise nonuniformly and singly in the case of irradiations at a low dose rate or fractionated irradiation to be reconverted to water increases. It may be that in the case of irradiation at a low dose rate, fewer intermediate substances capable of reaction are formed in the cellular water, since single radicals are more rapidly transformed into water.

In the case of densely ionizing radiation evidently the probability of recombination is increased, inasmuch as the events rapidly follow one another, and a decrease in the dose rate is insufficient to promote recovery. It may be that the radicals of neutron-irradiated water molecules, even in the case of low radiation intensity, are arranged densely and uniformly, then forming effective peroxides [25].

Influence of dose rate on the RBE. It should be mentioned that, in spite of the large number of studies on the influence of the dose rate that have appeared lately, the proportion of studies of the relationship between the RBE and time factor is relatively small, although from the radiobiological standpoint it is important to determine whether the RBE of one type of radiation or another depends upon the dose rate.

Chronic, acute, and pulsed influences are customarily distinguished, depending upon the dose rate used.

Chronic influence. Irradiation is performed continuously at a very low dose rate. The basic studies conducted up to 1955 are generalized in Raevskiy's book [29]. The author, analyzing these investigations, arrived at the conclusion that there is a definite relationship between the RBE and the time factor.

Evans [30] proposed that the RBE of fast neutrons, in a comparison of their effects on mammals with the effects of X-rays under conditions of a decrease in the daily dose to the maximum permissible level, increases. A similar view is also maintained by other authors [13].

The investigation of Upton et al. [30] was devoted to a study of the influence of various dose rates (100 and 7×10^{-5} rad/min) on the RBE of neutrons with energies of 1.5 and 14 MeV in comparison with γ radiation on mice. The criteria of injurious effect were lifetime, formation of tumors, opacification of the crystalline lens, aging and other degenerative changes. The value of the RBE of fast neutrons increased with decreasing dose rate according to the criterion of lifetime. This is due to a substantial decrease in the effectiveness of γ rays with decreasing dose rate.

According to the observations of Searle and Phillips [32], the RBE of neutrons at a dose rate of 0.01 rad/min with respect to the induction of dominant lethals in the spermatozoa of male mice in comparison with X-rays proved equal to six; when the neutron dose rate was increased by three orders of magnitude (50 rad/min), the effectiveness of the neutrons was unchanged.

In the experiments of Neary et al. [33] studying the fertility of female mice, it was shown that when the duration of irradiation was increased

from 10 to 20 weeks, the value of the RBE was unchanged. In an experiment on the decrease in the weight of the testes of mice, the RBE in the case of irradiation for 24 hours was approximately the same as in the case of irradiation for a little more than seven months, with a considerably lower dose rate. From the standpoint of the data of the authors, these experiments are evidence of an identical rate of the processes of recovery in the systems studied under the influence of X-rays and neutrons.

We compared the results of several authors on the influence of the time factor upon the RBE, obtained according to various indices on mice (Table). On the basis of an analysis of these materials, we can conclude that the effects of the dose rate upon the RBE are not the same when different responses of the organism are evaluated.

Table

Dependence of the RBE on the Time Factor

(1) Сравниваемые излучения	(2) Исследуемый показатель	(3) Значение коэффициента ОБЭ				(8) Литература
		кратковременное (4)	мощность дозы, рад/мин (5)	длительное (6)	мощность дозы, рад/сутки (7)	
(9) Быстрые нейтроны (10) Рентгеновские лучи	(13) Смертность	3 —	— —	5 10	11 1	[29] [34]
(9) Быстрые нейтроны (10) Рентгеновские лучи	(14) Сокращение продолжительности жизни	2—5	—	10—15	—	[35]
(11) α-Частицы (10) Рентгеновские лучи	(13) Смертность	2	—	10	10	[29]
(9) Быстрые нейтроны (12) γ-Излучение Co^{60}	(15) Понижение плодовитости	5—6 —	3,7—120 —	— 6—7	— 1	[36] [34]
(9) Быстрые нейтроны (12) γ-Излучения Co^{60}	Уменьшение веса семенников (16)	6 —	3,7—120 —	— 7	— 1	[36] [34]

Key to Table: 1) radiations compared; 2) index investigated; 3) RBE; 4) short term; 5) dose rate, rad/min; 6) long term; 7) dose rate, rad/day; 8) literature reference; 9) fast neutrons; 10) X-rays; 11) α particles; 12) γ radiation of Co^{60}; 13) death rate; 14) reduction of lifetime; 15) decrease in fertility; 16) decrease in weight of testes.

Some data on the influence of the dose rate are contained in the report of the RBE Committee [18].

Damage to the cells of mammals and various other systems by radiation with low LEL usually depends upon the dose rate and does not show a simple exponential dose-effect dependence. Exceptions are irradiations at low dose rates and in low doses. The increase in the RBE in the case of long-term irradiation shows that the effectiveness of radiation with a high LEL with

respect to the decrease in lifetime depends negligibly upon the dose rate, whereas the effectiveness of radiation with low LEL decreases with increasing dose rate, at least two to three-fold in the range of dose rates studied.

On the basis of a generalization of the experimental data, the authors of [18] arrived at the following conclusion: when there is a dependence on the dose rate, for radiation with high LEL, this dependence is less pronounced (Fig. 3).

Acute influences. Irradiation is completed in a short period of time; the values of the dose in this case may reach hundreds of rad and cause early somatic injuries, such as the acute radiation syndrome and local injuries.

Under these conditions, an influence of the dose rate on the RBE is also noted. Thus, the value of the RBE with respect to $LD_{50/30}$ in mice for acute neutron irradiation (exposure 1.5 hrs) in comparison with γ irradiation is equal to 4.4, while in the case of prolonged irradiation (24 hr exposure) it is equal to 6.3 [37]. This may be explained by the fact that the effectiveness of γ radiation drops as the dose rate decreases.

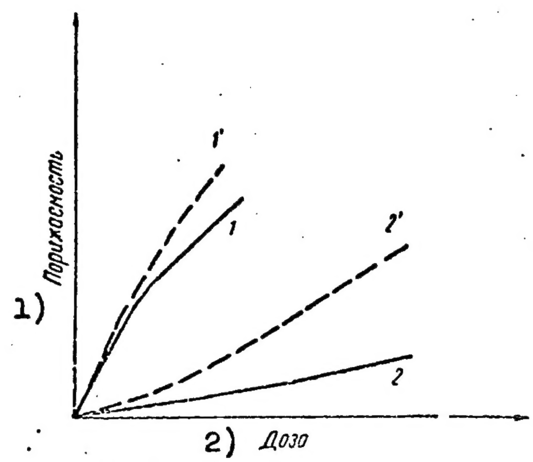

Fig. 3. Dose-effect curves for radiations with low and high LEL: 1 -- radiation with high LEL (curve 1' shows the increase in vulnerability with increasing dose rate); 2 -- radiation with low LEL (curve 2' shows the increase in vulnerability with increasing dose rate).
Key: 1) Vulnerability; 2) dose.

An influence of the dose rate was also noted under the action of high-energy X-ray radiation (E = 22 MeV, LEL = 0.2 keV/μ) [38, 39]. The value of the RBE in this case, in comparison with 400 kV X-ray radiation in an acute influence is equal to 0.75, while in the case of irradiation at a dose rate of 250 R/day it is 1.09.

Pulsed influence. This is irradiation by single pulses of short duration at a high dose rate (up to 10^8-10^9 rad/sec). Radiobiological experiments in which pulsed tubes were used, providing X-ray flashes with a duration of 1 μ/sec, were first described by Kingdom et al. [40]. In these experiments,

the intensity of a single X-ray pulse was very low (tenths of a roentgen). To obtain doses of hundreds of roentgens, it was necessary to produce hundreds of flashes, and this approached the conditions of ultrafractionated irradiation.

In recent years, pulsed reactors have been used as sources of single pulses. Spalding et al. [28] conducted total irradiation of four-month old female mice by fission neutrons on the "Godiva" reactor, working in a pulsed system. The animals were irradiated at doses of 183-474 rad (per pulse) at a dose rate of $2 \cdot 10^8$ rad/min; simultaneously another group of mice of the same line and the same age were irradiated with the γ radiation of Co^{60} at a dose rate of 9 rad/min. The value of $LD_{50/30}$ for fission neutrons proved equal to 193±9.7 rad in the first case and 739±19 rad in the second. The value of the RBE of fission neutrons in comparison with the o radiation of Co^{60} according to this index was equal to 3.6. Under the conditions of this experiment, the value of $LD_{50/30}$ did not depend upon the neutron dose rate within the interval $10\text{-}2 \cdot 10^{18}$ rad/min. On the basis of the complete correspondence of the results of these investigations to the observations of Storer [41], who worked with even lower neutron dose rates (0.15 rad/min), the authors conclude that the effect of neutrons is independent of the dose rate within the interval $0.15\text{-}2{:}10^8$ rad/min. Consequently, the change in the RBE under these conditions depends upon the influence of the dose rate upon the biological effect of γ radiation, with which the comparison is made.

Influence of fractionation of the dose on the RBE coefficients. In radiobiology, one distinguishes fractionated and ultrafractionated influences.

In the case of fractionated influence, the total dose is divided into parts; moreover, fractions differing in dose and dose rates, as well as with different intervals between them, are possible.

Melvill et al. [42] determined the values of $LD_{50/30}$ of mice, by fractionally irradiating them with X-rays and fast neutrons. The influence was repeated on the second, fourth, fifth, sixth, and eighth days after the first irradiation. The authors observed no changes in the RBE coefficient in the case of fractionation. In all cases the RBE of fast neutrons remained equal to approximately one with respect to the $LD_{50/30}$ for mice.

In the work of Yu. G. Grigor'yev et al. [43], the RBE of high-energy protons (510, 126 MeV) were studied in single and fractional irradiations of dogs. In the case of single irradiation at doses of 250-550 rad, the RBE for 510 MeV protons was equal to 1.15, and for 126 MeV protons -- 1.0. In the case of fractional irradiation of the animals at the same dose, the RBE for both proton energies proved equal to 1.0.

Fogel et al. [44] compared the influence of irradiation by fission neutrons and by the γ rays of Co^{60} for 13 weeks on the survival rate of female mice. The dose rate was equal to approximately 0.75 rad/min for neutrons and 0.25 rad/min for γ rays. The data obtained by these authors show that under conditions of fractionated irradiation, the RBE of fission neutrons varies little.

In the case of ultrafractionation, the radiation influence is accomplished by an interrupted flux of particles or quanta, coming in pulses with a duration of several micro- or milliseconds and at intervals of various durations (within the limits of a second) [45]. Lotz et al. [46] propose that

irradiation in which the duration of the pulse and the pause is shorter than the time constants of biological and physical processes be considered as ultrafractionated.

The systematic study of the relationship between the ultrafractionated influence and the biological effect was begun after accelerators generating pulsed radiation were designed. Most of the researchers used lower living organisms as specimens, and only individual studies have been conducted on mammals. The influence of ultrafractionation on damage to ascites carcinoma, grafted into mice, was studied by Hoffmann and Kepp [47].* In these

*X-ray radiation (60 kV) and the β radiation of Sr^{90} were used as the sources.

investigations it was shown that the effect depends upon the parameters of the ultrafractionation.

Müller and Hase [48], who conducted experiments with ultrafractionated irradiation of Drosophila eggs with the β particles of radium, arrived at the conclusion that the biological effect in this case is decreased in comparison with continuous irradiation. They obtained the maximum effect at a frequency of 590 counts/sec. According to their data, it can be judged that with an unchanged ratio of the time of influence to the time of the pause (1:2), the RBE of the β radiation of radium with respect to the death of Drosophila eggs increases with increasing frequency.

An opposite effect for the same experimental conditions but for coli bacteria was obtained by Diecmann [49].

In a comparison of the injurious effect of the β radiation of Sr^{90} and of X-rays (60 kV) on fruit-fly eggs, Hofmann [47] found that in all cases X-rays were two to three times as effective. This relationship was practically unchanged with changing ratios of the time of the pulse to the time of the pause, but in this case the effect from X-rays increased distinctly with increasing quotient of the division of the time of the pulse into the time of the pause, whereas the effect from the influence of β radiation drops quite correspondingly. Thus, in this case dynamic constancy of the coefficient, demonstrating the lower effectiveness of β particles, was observed.

Influence of the Macro- and Microspatial Distribution of the Absorbed Dose on the Values of the RBE Coefficients

In setting up experiments to study the RBE of various types of radiations, identical space distributions of the dose for the radiations compared must be achieved. The first approximation to the fulfillment of this condition is the creation of a uniform field of the required dimensions.

Nuclear reactors and accelerators are usually used as radiation sources with high LEL. The difficulties in the creation of uniform fields of irradiation in this case are associated with the fact that beams of particles on accelerators, as a rule, are narrow and unsuitable for the total irradiation of large animals. The work of V. P. Afanas'yev et al. [50] cites